

AMENDMENTS

CLAIMS

1. (currently amended) A method for determining the propensity of a test compound to cause depletion of reticulocytes in a subject, the method comprising:
 - a) administering an effective amount of a test compound to a test subject for a selected period of time;
 - b) determining the expression level of a plurality of indicator genes, wherein said indicator genes exhibit a statistically significant change in expression level in response to administration of a plurality of compounds known to cause depletion of reticulocytes in a test subject;
 - c) determining the difference between the expression level of each indicator gene and a control expression level of said indicator gene;
 - d) determining the statistical significance of the difference between the expression level of each indicator gene and a control expression level of said indicator gene;
 - e) assigning a probability of reticulocyte depletion in response to said test compound if a ~~substantial~~ fraction of said plurality of said indicator genes exhibit a statistically significant change in expression level.
2. (original) The method of claim 1, wherein said selected period of time is three days.
3. (original) The method of claim 1, wherein said selected period of time is five days.
4. (withdrawn) A Drug Signature database, comprising:
a plurality of Drug Signature records, wherein each Drug Signature record comprises
indicia of one compound;
indicia of a set of genes that are upregulated in response to administration of said compound, wherein said set of genes distinguishes said compound from all other compounds within said Drug Signature database,
further comprising a Reticulocyte Depletion Signature.

5. (withdrawn) A method for deriving a Reticulocyte Depletion Signature, the method comprising:

a) administering an effective amount of a plurality of compounds to test subjects for a selected period of time, said plurality of compounds comprising a plurality of bone marrow toxicants or immunosuppressants that cause reticulocyte depletion and a plurality of control compounds;

b) identifying a plurality of affected genes, wherein said affected genes exhibit a statistically significant change in expression level in response to administration of said plurality of non-steroidal anti-inflammatory drugs compared to said control compounds; and

c) identifying the affected genes for which the difference in expression level is statistically significant.

6. (currently amended) The method of claim 1, wherein said probability is evaluated by any one of the following methods; Euclidian distance, Pearson's correlation coefficient, or Signature Projection Score. ~~the method comprising:~~

~~a) deriving a test compound vector representing the expression of said indicator genes in response to said test compound; and~~

~~b) projecting said test compound vector against a signature vector representing the expression of said indicator genes in response to a plurality of compounds known to cause reticulocyte depletion;~~

~~wherein the degree of match between the test compound vector and the signature vector indicates the degree to which the test compound will exhibit reticulocyte depletion characteristic of the compounds used to derive the signature vector.~~

7. (previously presented) The method of claim 1 wherein said plurality of indicator genes comprises aminolevulinate synthase 2 and peripherin.

8 (new) The method of claim 1, wherein said probability is assigned by calculating the Signature Projection Score (SPS) for the test expression response under a dose/time treatment of

said test compound,

$$SPS(C) = \max_{c \in C} \left\{ \sum_{g \in G_s} \frac{(X_g^c - R_g)(T_g - R_g)}{S_g} \right\}$$

where X_g^c is the test expression response, for selected gene g ,

T_g is the expression response for reticulocyte depletion, for selected gene g

R_g is the reference gene expression levels, for selected gene g and

S_g is the scaling factor for the contribution of each gene to the signature score,

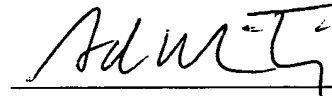
whereby the SPS for said test compound indicates the probability of reticulocyte depletion in a test subject.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 798-3547.

Respectfully submitted,

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Adam Whiting (Reg. No. 44,400)
Elisabeth Evertsz (Reg. No. 50,304)

HOWREY LLP
2941 Fairview Park Drive
Box 7
Falls Church, VA 22042
Fax (650) 798-3547
Ph. (650) 798-3600